REMARKS

Applicants amended claims 1, 2, 3, 4 and 6 to improve their form. Support for the amendments is found in the specification, considered as a whole, e.g., at pages 3, 6 and 7, paragraphs 0021, 0028 and 0029 of U.S. Patent Application Publication No. 2006/0189696.

SUBSTANCE OF TELEPHONE INTERVIEWS

Applicants express their appreciation to the Examiner for granting them on October 18 and during the week of November 26, 2007, telephone interviews. On October 18, 2007 Applicants' undersigned Counsel sought confirmation regarding the indication of novelty of the elected group and species. The Examiner confirmed that the elected Group I (claims 1-7) and the first species, sub-parts a) and d) of claim 1, are novel, and that the cancellation of sub-parts b) and c) of claim 1, should place claim 1 in condition for allowance.

Applicants' Counsel contacted the Examiner during the week of November 26, 2007 to seek clarification of the assertion in the Office Action that the oath or declaration was detective because Prof. Dionysios Tsambaos has not signed the oath. Counsel pointed out that a Petition Under 37 CFR 1.47 was filed on September 20, 2005 requesting acceptance of the application without signature of Prof. Tsambaos, including a Declaration executed by Prof. Tsambaos on September 5, 2005. The Examiner advised that he reviewed the Petition and believes it is sufficient to satisfy the requirements of 37 C.F.R. § 1.47, and thus no oath executed by Prof. Tsambaos is needed. Nonetheless, Applicants also faxed on December 7, 2007, a copy of the Petition and the Declaration to the PCT Legal Office to seek clarification of status of the Petition since no decision on the Petition has been received.

ELECTION/RESTRICTIONS

Applicants' election with traverse of Group I in the August 22, 2007 reply was acknowledged, but was not found persuasive, and thus the restriction and election of species requirement were made Final. Office Action, page 2. Applicants continue to traverse the

restriction and election of species requirements, for all of the reasons set forth in the August 22, 2007 reply. Additionally, if a generic claim is found allowable, Applicants preserve their rights to request re-joinder of the non-elected claims and species.

CLAIM OBJECTIONS

Claim 1 was objected to because it contained non-elected subject matter, i.e., sub-parts b) and c) as discussed in the October 18, 2007 telephone interview. Applicants amended claim 1 to delete such subject matter. Thus, Applicants respectfully submit that claim 1 is in condition for allowance, as discussed at the interview, an indication of which is requested.

OATH/DECLARATION

The Declaration was asserted to be defective and the new oath or declaration was required.

Consistent with the interview during the week of November 26, 2007, Applicants enclose a supplemental Declaration (Appendix A) executed by two of the inventors, Messr. Dionysios Papaioannou and Dionysios Drainas, which indicates the citizenship of all inventors. Applicants also enclose an Application Data Sheet (Appendix A) which includes all the other requested information.

OBJECTIONS TO SPECIFICATION

The Examiner requested that Applicants capitalize the Buchi, Perkin-Elmer and Brucker trademarks and add generic terminology for the apparatus designated by these trademarks. Office Action, page 3.

Applicants respectfully point out that the three trademarks are capitalized; the Perkin-Elmer apparatus is a spectrophotometer and the Bruker apparatus a spectrometer, as set forth in the specification. As is known in the art, the Buchi SMP-20 apparatus is a very common

apparatus used in many Organic Chemistry Laboratories worldwide for the fast evaporation of volatile solvents under reduced pressure. It is technically described as a "rotary evaporator".

REJECTIONS UNDER 35 U.S.C. 112, FIRST PARAGRAPH

Claim 7 was rejected under 35 U.S.C. 112, first paragraph, because it was asserted that the specification, while enabling for compounds and methods of making them, does not reasonably provide enablement for pharmaceutical compositions comprising such compounds. In summary, it was asserted that *in vitro* testing of the compounds of the invention is insufficient to establish they work *in vivo*. In support of this rejection, the Office Action relied on Giuseppe et al., *Expert Opinion on Therapeutic Patents*, 1997, 7 (4) 307-323, which, it was asserted, discusses unpredictability of predicting the efficacy of a compound working *in vitro* and *in vivo,* page 4 of the Office Action. It was also asserted that Applicants did not show in the specification products with inert carriers, excipients, or adjuvants, nor that "...these compounds can be present in compositions, and are thus not enabled for compositions." The factors of *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) were quoted and relied upon as a further justification for the rejection. Office Action, pages 4-5. It was concluded that, based on Giuseppe et al., and the state of the art, apparently based solely on Giuseppe et al., and the lack of guidance provided in the specification, persons of ordinary skill in the art would be unduly burdened with experimentation to practice the invention commensurate with scope of the claims. Office Action, page 5.

Applicants respectfully traverse this rejection and submit that their specification enables persons of ordinary skill in the art how to make and use the full scope of the claimed invention.

It is well established that the enablement is judged from the perspective of a person of ordinary skill in the art. *See Falkner et al. v. Inglis et al.*, 448F.3d 1357, 1365, 79 USPQ2d 1001 (CAFC 2006), and MPEP, §2164.05(b).

Furthermore, in *Falkner*, the CAFC agreed with the holding of the U.S. Patent and Trademark Office Board of Patent Appeals and Interferences ("Board") that "the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion

that such experimentation would have been considered to be 'undue' in this art. Indeed, great expenditures of time and effort were ordinary in the field of vaccine preparation." *Id.*

Also, see *Johns Hopkins University v. Cellpro Inc.,* 47 U.S.P.Q.2d 1705 (Fed. Cir. 1998), wherein the Federal Circuit found enablement in a patent specification disclosing only one method of producing one antibody for a claim directed to a broader genus of antibodies. The court made that finding based, *inter alia*, on a Declaration submitted by an opposing party's (a defendant in a patent infringement litigation) expert that the disclosure of the specification of the patent was sufficient for him to make antibodies other than that disclosed in the specification. The expert stated in the Declaration that he had to use some experimentation to obtain that result. The court concluded that such routine experimentation does not constitute undue experimentation. *Johns Hopkins, Id.* at 1718-19. Also see *Falkner et al. v. Inglis et al.,* 448 F.3d 1357, 79 U.S.P.Q.2d 1001, 05-1324 (Fed. Cir. 2006).

The rejection was further premised on the assertion that, as mentioned above "applicants do not show compositions of the products with inner carriers, excipients, or adjuvants, is not shown in the specification. Applicants do not show that these compounds can be present in compositions, and are thus not enabled for compositions". Page 4 of the Office Action. The use of such carriers, excipients or adjuvants is well known in the pharmaceutical industry. For example, see the attached literature (SPCs) on two acidic retinoid-based pharmaceutical compositions, Roaccutane and Neotigason, including a list of excipients for both. (Appendix B) It is well established that that which is known in the art need not be included in a patent application to enable the claimed invention.

As stated in the MPEP,

> "If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied. For example, it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation,

this would be sufficient to satisfy 35 U.S.C. 112, first paragraph. " *See* MPEP, § 2164.01(c) (Citations to court decisions omitted.).

Based on Applicants' disclosure and the knowledge of persons of ordinary skill in the art, such persons would be readily able to provide suitable carriers, adjuvants or excipients, if needed, to formulate a pharmaceutical preparation or product of claim 7.

Claim 3 was rejected under U.S.C. 112, first paragraph, allegedly because the specification does not reasonably provide enablement for the use of any tertiary amine. Office Action, pages 5-7.

Applicants respectfully traverse this assertion and submit that claim 3, prior to its amendment herein, was enabled. Nonetheless in the interest of expediting prosecution Applicants amended their claim 3, which continues to be enabled.

REJECTIONS UNDER 35 U.S.C. 112, SECOND PARAGRAPH

Claims 2-6 were rejected under 35 U.S.C. 112, second paragraph, for several reasons. Office Action, page 7. Applicants submit that these claims were definite, prior to their amendment herein, because persons of ordinary skill in the art would have been able to easily understand the metes and bounds the claimed subject matter of those claims. In the interest of expediting prosecution Applicants amended claims 2-6, which continue to be definite.

CLAIM OBJECTIONS

Claim 6 was objected to as being in improper form because of a multiple dependency recitation. Applicants' amended claim 6 is free of this informality.

INDICATION OF ALLOWABLE SUBJECT MATTER

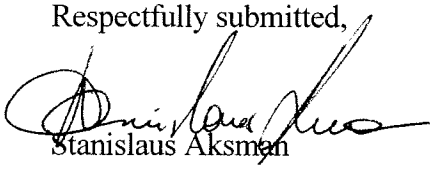
Applicants appreciate the indication, at page 8 of the Office Action, that the elected group and species are considered novel.

CONCLUSION

For all the reasons detailed above, all claims in the Application are in condition of allowance, an indication of which is respectfully solicited. In the event any outstanding issues remain, Applicants would appreciate the courtesy of a telephone call to the undersigned Counsel to resolve such issues in an expeditious and effective manner to place the application in condition for allowance.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 50-2478 and please credit any excess fees to such deposit account.

Respectfully submitted,



Stanislaus Aksman
Registration No. 28,562

Roberts Mlotkowski & Hobbes P.C.
Intellectual Property Department
P.O. Box 10064
McLean, VA 22102
Telephone: 703-584-3270
Facsimile: 703-848-2981
January 17, 2008

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76) AND POWER OF ATTORNEY

Title of Invention	Polyamine Conjugates With Acidic Retinoids and Preparation Thereof

As the below named inventor(s), I/we declare that:

This declaration is directed to:

☐ The attached application, or

☒ Application No. 10/549,905, filed on September 20, 2005,

☐ as amended on _____ _____ (if applicable);

I/We believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought;

I/We have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

I/We acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT International filing date of the continuation-in-part application.

All statements made herein of my/own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

I/We hereby appoint:

Practitioners at Customer Number 25570 as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

FULL NAME OF INVENTOR(S)

Inventor one: Dionysios Papaioannou

Signature: _____ Citizen of: Greece

Inventor two: Dionysios Dranas

Signature: _____ Citizen of: Greece

Inventor three: Dionysios Tsambaos

Signature: _____ Citizen of: Greece

Inventor four: _____

Signature: _____ Citizen of: _____

APPENDIX A

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	13907-02
	Application Number	
Title of Invention	POLYAMINE CONJUGATES WITH ACIDIC RETINOIDS AND PREPARATION THEREOF	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Dionysios		PAPAIOANNOU	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Patras	Country Of Residence[i]	GR

Citizenship under 37 CFR 1.41(b) [i] GR

Mailing Address of Applicant:

Address 1	University of Patras
Address 2	Department of Chemistry

City	Patras	State/Province	
Postal Code	26504	Country[i]	GR

Applicant 2

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Dionysios		DRAINAS	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Patras	Country Of Residence[i]	GR

Citizenship under 37 CFR 1.41(b) [i] GR

Mailing Address of Applicant:

Address 1	University of Patras
Address 2	School of Medicine, Department of Biochemistry

City	Patras	State/Province	
Postal Code	26504	Country[i]	GR

Applicant 3

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Dionysios		TSAMBAOS	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Patras	Country Of Residence[i]	GR

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	13907-02
	Application Number	
Title of Invention	POLYAMINE CONJUGATES WITH ACIDIC RETINOIDS AND PREPARATION THEREOF	

Citizenship under 37 CFR 1.41(b) [i]	GR		
Mailing Address of Applicant:			
Address 1	University of Patras		
Address 2	Department of Dermatology, School of Medicine		
City	Rio Patras	**State/Province**	
Postal Code	26504	**Country** [i]	GR

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	25570		
Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	POLYAMINE CONJUGATES WITH ACIDIC RETINOIDS AND PREPARATION THEREOF		
Attorney Docket Number	13907-02	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	12	**Suggested Figure for Publication (if any)**	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S. C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	13907-02
	Application Number	

Title of Invention	POLYAMINE CONJUGATES WITH ACIDIC RETINOIDS AND PREPARATION THEREOF

Customer Number	25570

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	a 371 of international	PCT/GR2002/000045	2002-08-22

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

			Remove
Application Number	Country [i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			◯ Yes ◯ No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1

If the Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information:

Address 1			
Address 2			
City		**State/Province**	
Country [i]		Postal Code	
Phone Number		Fax Number	
Email Address			

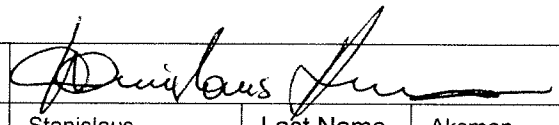
Additional Assignee Data may be generated within this form by selecting the **Add** button.

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	13907-02
	Application Number	
Title of Invention	POLYAMINE CONJUGATES WITH ACIDIC RETINOIDS AND PREPARATION THEREOF	

Signature				Date (YYYY-MM-DD)	2008-01-17
First Name	Stanislaus	Last Name	Aksman	Registration Number	28562

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

APPENDIX B

Roche Products Limited

Hexagon Place
6 Falcon Way
Shire Park
Welwyn Garden City
Hertfordshire
AL7 1TW

Telephone:	**+44 (0)1707 366 000**
Facsimile:	**+44 (0)1707 338 297**
WWW:	**http://www.rocheuk.com/**
Medical Information direct line:	**+44 (0)800 032 7298**
Customer Care direct line:	**+44 (0)800 731 5711**
Medical Information e-mail:	**roche@professionalinformation.co.uk**
Medical Information facsimile:	**+44 (0)1748 828801**

Document last updated on the *e*MC: **Fri 09 February 2007**

Roaccutane

Table of Contents

1. NAME OF THE MEDICINAL PRODUCT
2. QUALITATIVE AND QUANTITATIVE COMPOSITION
3. PHARMACEUTICAL FORM
4. CLINICAL PARTICULARS
4.1 Therapeutic indications
4.2 Posology and method of administration
4.3 Contraindications
4.4 Special warnings and precautions for use
4.5 Interaction with other medicinal products and other forms of interaction
4.6 Pregnancy and lactation
4.7 Effects on ability to drive and use machines
4.8 Undesirable effects
4.9 Overdose
5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
5.2 Pharmacokinetic properties
5.3 Preclinical safety data
6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
6.2 Incompatibilities
6.3 Shelf life
6.4 Special precautions for storage
6.5 Nature and contents of container
6.6 Special precautions for disposal and other handling
7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10. DATE OF REVISION OF THE TEXT
LEGAL STATUS

1. NAME OF THE MEDICINAL PRODUCT

Roaccutane 5 mg soft capsules

Roaccutane 20 mg soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 5 mg or 20 mg of isotretinoin

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules, soft

5mg capsule: Oval, opaque, pale red-violet and white capsules imprinted with R5 in black ink.

20mg capsule: Oval, opaque, pale red-violet and white capsules imprinted with ROA 20 in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.

4.2 Posology and method of administration

Isotretinoin should only be prescribed by or under the supervision of physicians with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements.

The capsules should be taken with food once or twice daily.

Adults including adolescents and the elderly:

Isotretinoin therapy should be started at a dose of 0.5 mg/kg daily. The

therapeutic response to isotretinoin and some of the adverse effects are dose-related and vary between patients. This necessitates individual dosage adjustment during therapy. For most patients, the dose ranges from 0.5-1.0 mg/kg per day.

Long-term remission and relapse rates are more closely related to the total dose administered than to either duration of treatment or daily dose. It has been shown that no substantial additional benefit is to be expected beyond a cumulative treatment dose of 120-150 mg/kg. The duration of treatment will depend on the individual daily dose. A treatment course of 16-24 weeks is normally sufficient to achieve remission.

In the majority of patients, complete clearing of the acne is obtained with a single treatment course. In the event of a definite relapse a further course of isotretinoin therapy may be considered using the same daily dose and cumulative treatment dose. As further improvement of the acne can be observed up to 8 weeks after discontinuation of treatment, a further course of treatment should not be considered until at least this period has elapsed.

Patients with severe renal insufficiency

In patients with severe renal insufficiency treatment should be started at a lower dose (e.g. 10 mg/day). The dose should then be increased up to 1 mg/kg/day or until the patient is receiving the maximum tolerated dose (see section 4.4).

Children

Isotretinoin is not indicated for the treatment of prepubertal acne and is not recommended in patients less than 12 years of age.

Patients with intolerance

In patients who show severe intolerance to the recommended dose, treatment may be continued at a lower dose with the consequences of a longer therapy duration and a higher risk of relapse. In order to achieve the maximum possible efficacy in these patients the dose should normally be continued at the highest tolerated dose.

4.3 Contraindications

Isotretinoin is contraindicated in women who are pregnant or breastfeeding. (see section 4.6).

Isotretinoin is contraindicated in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see section 4.4).

Isotretinoin is also contraindicated in patients with hypersensitivity to isotretinoin or to any of the excipients. Roaccutane contains arachis oil (peanut oil), soya oil, partially hydrogenated soya oil, and hydrogenated soya oil. Therefore, Roaccutane is contraindicated in patients allergic to peanut or soya.

Isotretinoin is also contraindicated in patients

- With hepatic insufficiency
- With excessively elevated blood lipid values
- With hypervitaminosis A
- Receiving concomitant treatment with tetracyclines (see section 4.5)

4.4 Special warnings and precautions for use

Pregnancy Prevention Programme

This medicinal product is TERATOGENIC

Isotretinoin is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Programme are met:

- She has severe acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy (see section 4.1).
- She understands the teratogenic risk.
- She understands the need for rigorous follow-up, on a monthly basis.
- She understands and accepts the need for effective contraception, without interruption, 1 month before starting treatment, throughout the duration of treatment and 1 month after the end of treatment. At least one and preferably two complementary forms of contraception including a barrier method should be used.
- Even if she has amenorrhea she must follow all of the advice on effective contraception.
- She should be capable of complying with effective contraceptive measures.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy.
- She understands the need and accepts to undergo pregnancy testing before, during and 5 weeks after the end of treatment.
- She has acknowledged that she has understood the hazards and necessary precautions associated with the use of isotretinoin.

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

The prescriber must ensure that:

• The patient complies with the conditions for pregnancy prevention as listed above, including confirmation that she has an adequate level of understanding.

• The patient has acknowledged the aforementioned conditions.

• The patient has used at least one and preferably two methods of effective contraception including a barrier method for at least 1 month prior to starting treatment and is continuing to use effective contraception throughout the treatment period and for at least 1 month after cessation of treatment.

• Negative pregnancy test results have been obtained before, during and 5 weeks after the end of treatment. The dates and results of pregnancy tests should be documented.

Contraception

Female patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception.

As a minimum requirement, female patients at potential risk of pregnancy must use at least one effective method of contraception. Preferably the patient should use two complementary forms of contraception including a barrier method. Contraception should be continued for at least 1 month after stopping treatment with isotretinoin, even in patients with amenorrhea.

Pregnancy testing

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25mIU/mL are recommended to be performed in the first 3 days of the menstrual cycle, as follows.

Prior to starting therapy:

In order to exclude the possibility of pregnancy prior to starting contraception, it is recommended that an initial medically supervised pregnancy test should be performed and its date and result recorded. In patients without regular menses, the timing of this pregnancy test should reflect the sexual activity of the patient and should be undertaken approximately 3 weeks after the patient last had unprotected sexual intercourse. The prescriber should educate the patient about contraception.

A medically supervised pregnancy test should also be performed during the consultation when isotretinoin is prescribed or in the 3 days prior to the visit to the prescriber, and should have been delayed until the patient had been using effective contraception for at least 1 month. This test should ensure the patient is not pregnant when she starts treatment with isotretinoin.

Follow-up visits

Follow-up visits should be arranged at 28 day intervals. The need for repeated medically supervised pregnancy tests every month should be determined

according to local practice including consideration of the patient's sexual activity and recent menstrual history (abnormal menses, missed periods or amenorrhea). Where indicated, follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

End of treatment

Five weeks after stopping treatment, women should undergo a final pregnancy test to exclude pregnancy.

Prescribing and dispensing restrictions

Prescriptions of isotretinoin for women of childbearing potential should be limited to 30 days of treatment and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing of isotretinoin should occur on the same day. Dispensing of isotretinoin should occur within a maximum of 7 days of the prescription.

Male patients:

The available data suggest that the level of maternal exposure from the semen of the patients receiving isotretinoin, is not of a sufficient magnitude to be associated with the teratogenic effects of isotretinoin. Male patients should be reminded that they must not share their medication with anyone, particularly not females.

Additional precautions

Patients should be instructed never to give this medicinal product to another person, and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy and for 1 month following discontinuation of isotretinoin because of the potential risk to the foetus of a pregnant transfusion recipient.

Educational material

In order to assist prescribers, pharmacists and patients in avoiding foetal exposure to isotretinoin the Marketing Authorisation Holder will provide educational material to reinforce the warnings about the teratogenicity of isotretinoin, to provide advice on contraception before therapy is started and to provide guidance on the need for pregnancy testing.

Full patient information about the teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme should be given by the physician to all patients, both male and female.

Psychiatric disorders

Depression, depression aggravated, anxiety, aggressive tendencies, mood alterations, psychotic symptoms, and very rarely, suicidal ideation, suicide

attempts and suicide have been reported in patients treated with isotretinoin (see section 4.8). Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary. However, discontinuation of isotretinoin may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

Skin and subcutaneous tissues disorders

Acute exacerbation of acne is occasionally seen during the initial period but this subsides with continued treatment, usually within 7 - 10 days, and usually does not require dose adjustment.

Exposure to intense sunlight or to UV rays should be avoided. Where necessary a sun-protection product with a high protection factor of at least SPF 15 should be used.

Aggressive chemical dermabrasion and cutaneous laser treatment should be avoided in patients on isotretinoin for a period of 5-6 months after the end of the treatment because of the risk of hypertrophic scarring in atypical areas and more rarely post inflammatory hyper or hypopigmentation in treated areas. Wax depilation should be avoided in patients on isotretinoin for at least a period of 6 months after treatment because of the risk of epidermal stripping.

Concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase (see section 4.5).

Patients should be advised to use a skin moisturising ointment or cream and a lip balm from the start of treatment as isotretinoin is likely to cause dryness of the skin and lips.

Eye disorders

Dry eyes, corneal opacities, decreased night vision and keratitis usually resolve after discontinuation of therapy. Dry eyes can be helped by the application of a lubricating eye ointment or by the application of tear replacement therapy. Intolerance to contact lenses may occur which may necessitate the patient to wear glasses during treatment.

Decreased night vision has also been reported and the onset in some patients was sudden (see section 4.7). Patients experiencing visual difficulties should be referred for an expert ophthalmological opinion. Withdrawal of isotretinoin may be necessary.

Musculo-skeletal and connective tissue disorders

Myalgia, arthralgia and increased serum creatine phosphokinase values have been reported in patients receiving isotretinoin, particularly in those undertaking vigorous physical activity (see section 4.8).

Bone changes including premature epiphyseal closure, hyperostosis, and

calcification of tendons and ligaments have occurred after several years of administration at very high doses for treating disorders of keratinisation. The dose levels, duration of treatment and total cumulative dose in these patients generally far exceeded those recommended for the treatment of acne.

Benign intracranial hypertension

Cases of benign intracranial hypertension have been reported, some of which involved concomitant use of tetracyclines (see section 4.3 and section 4.5). Signs and symptoms of benign intracranial hypertension include headache, nausea and vomiting, visual disturbances and papilloedema. Patients who develop benign intracranial hypertension should discontinue isotretinoin immediately.

Hepatobiliary disorders

Liver enzymes should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated. Transient and reversible increases in liver transaminases have been reported. In many cases these changes have been within the normal range and values have returned to baseline levels during treatment. However, in the event of persistent clinically relevant elevation of transaminase levels, reduction of the dose or discontinuation of treatment should be considered.

Renal insufficiency

Renal insufficiency and renal failure do not affect the pharmacokinetics of isotretinoin. Therefore, isotretinoin can be given to patients with renal insufficiency. However, it is recommended that patients are started on a low dose and titrated up to the maximum tolerated dose (see section 4.2).

Lipid Metabolism

Serum lipids (fasting values) should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated. Elevated serum lipid values usually return to normal on reduction of the dose or discontinuation of treatment and may also respond to dietary measures.

Isotretinoin has been associated with an increase in plasma triglyceride levels. Isotretinoin should be discontinued if hypertriglyceridaemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur (see section 4.8). Levels in excess of 800mg/dL or 9mmol/L are sometimes associated with acute pancreatitis, which may be fatal.

Gastrointestinal disorders

Isotretinoin has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. Patients experiencing severe (haemorrhagic) diarrhoea should discontinue isotretinoin immediately.

Allergic reactions

Anaphylactic reactions have been rarely reported, in some cases after previous topical exposure to retinoids. Allergic cutaneous reactions are reported infrequently. Serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement have been reported. Severe allergic reactions necessitate interruption of therapy and careful monitoring.

Fructose intolerance

Roaccutane contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

High Risk Patients

In patients with diabetes, obesity, alcoholism or a lipid metabolism disorder undergoing treatment with isotretinoin, more frequent checks of serum values for lipids and/or blood glucose may be necessary. Elevated fasting blood sugars have been reported, and new cases of diabetes have been diagnosed during isotretinoin therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Patients should not take vitamin A as concurrent medication due to the risk of developing hypervitaminosis A.

Cases of benign intracranial hypertension (pseudotumor cerebri) have been reported with concomitant use of isotretinoin and tetracyclines. Therefore, concomitant treatment with tetracyclines must be avoided (see section 4.3 and section 4.4).

Concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy is an absolute contraindication to treatment with isotretinoin (see section 4.3). If pregnancy does occur in spite of these precautions during treatment with isotretinoin or in the month following, there is a great risk of very severe and serious malformation of the foetus.

The foetal malformations associated with exposure to isotretinoin include central nervous system abnormalities (hydrocephalus, cerebellar malformation/abnormalities, microcephaly), facial dysmorphia, cleft palate, external ear abnormalities (absence of external ear, small or absent external

auditory canals), eye abnormalities (microphthalmia), cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects), thymus gland abnormality and parathyroid gland abnormalities. There is also an increased incidence of spontaneous abortion.

If pregnancy occurs in a woman treated with isotretinoin, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice.

Lactation:

Isotretinoin is highly lipophilic, therefore the passage of isotretinoin into human milk is very likely. Due to the potential for adverse effects in the child exposed via mothers' milk, the use of isotretinoin is contraindicated in nursing mothers.

4.7 Effects on ability to drive and use machines

A number of cases of decreased night vision have occurred during isotretinoin therapy and in rare instances have persisted after therapy (see section 4.4 and section 4.8). Because the onset in some patients was sudden, patients should be advised of this potential problem and warned to be cautious when driving or operating machines.

Drowsiness, dizziness and visual disturbances have been reported very rarely. Patients should be warned that if they experience these effects, they should not drive, operate machinery or take part in any other activities where the symptoms could put either themselves or others at risk.

4.8 Undesirable effects

Some of the side effects associated with the use of isotretinoin are dose-related. The side effects are generally reversible after altering the dose or discontinuation of treatment, however some may persist after treatment has stopped. The following symptoms are the most commonly reported undesirable effects with isotretinoin: dryness of the skin, dryness of the mucosae e.g. of the lips (cheilitis), the nasal mucosa (epistaxis), and the eyes (conjunctivitis).

Infections:	
Very Rare (□ 1/10 000)	Gram positive (mucocutaneous) bacterial infection
Blood and lymphatic system disorders:	
Very common (□ 1/10)	Anaemia, red blood cell sedimentation rate increased,

	thrombocytopenia, thrombocytosis
Common (☐ 1/100, < 1/10)	Neutropenia
Very Rare (☐ 1/10 000)	Lymphadenopathy
Immune system disorders:	
Rare (☐ 1/10 000,< 1/1000)	Allergic skin reaction, anaphylactic reactions, hypersensitivity
Metabolism and nutrition disorders:	
Very Rare (☐ 1/10 000)	Diabetes mellitus, hyperuricaemia
Psychiatric disorders:	
Rare (☐ 1/10 000,< 1/1000)	Depression, depression aggravated, aggressive tendencies, anxiety, mood alterations.
Very Rare (☐ 1/10 000)	Abnormal behaviour, psychotic disorder, suicidal ideation suicide attempt, suicide
Nervous system disorders:	
Common (☐ 1/100, < 1/10)	Headache
Very Rare (☐ 1/10 000)	Benign intracranial hypertension, convulsions, drowsiness, dizziness
Eye disorders:	
Very common (☐ 1/10)	Blepharitis, conjunctivitis, dry eye, eye irritation
Very Rare (☐ 1/10 000)	Blurred vision, cataract, colour blindness (colour vision deficiencies), contact lens intolerance, corneal opacity, decreased night vision, keratitis, papilloedema (as sign of benign intracranial hypertension), photophobia, visual disturbances.
Ear and labyrinth disorders:	
Very Rare (☐ 1/10 000)	Hearing impaired
Vascular disorders:	
Very Rare (☐ 1/10 000)	Vasculitis (for example Wegener's granulomatosis, allergic vasculitis)
Respiratory, thoracic and mediastinal disorders:	

Common (☐ 1/100, < 1/10)	Epistaxis, nasal dryness, nasopharyngitis
Very Rare (☐ 1/10 000)	Bronchospasm (particularly in patients with asthma), hoarseness
Gastrointestinal disorders:	
Very Rare (☐ 1/10 000)	Colitis, ileitis, dry throat, gastrointestinal haemorrhage, haemorrhagic diarrhoea and inflammatory bowel disease, nausea, pancreatitis (see section 4.4)
Hepatobiliary disorders:	
Very common (☐ 1/10)	Transaminase increased (see section 4.4)
Very Rare (☐ 1/10 000)	Hepatitis
Skin and subcutaneous tissues disorders:	
Very common (☐ 1/10)	Cheilitis, dermatitis, dry skin, localised exfoliation, pruritus, rash erythematous, skin fragility (risk of frictional trauma)
Rare (☐ 1/10 000,< 1/1000)	Alopecia
Very Rare (☐ 1/10 000)	Acne fulminans, acne aggravated (acne flare), erythema (facial), exanthema, hair disorders, hirsutism, nail dystrophy, paronychia, photosensitivity reaction, pyogenic granuloma, skin hyperpigmentation, sweating increased
Musculo-skeletal and connective tissue disorders:	
Very common (☐ 1/10)	Arthralgia, myalgia, back pain (particularly adolescent patients)
Very Rare (☐ 1/10 000)	Arthritis, calcinosis (calcification of ligaments and tendons), epiphyses premature fusion, exostosis, (hyperostosis), reduced bone density, tendonitis
Renal and urinary disorders:	
Very Rare (☐ 1/10 000)	Glomerulonephritis
General disorders and administration site conditions:	
Very Rare (☐ 1/10 000)	Granulation tissue (increased formation of),

	malaise
Investigations:	
Very common (☐ 1/10)	Blood triglycerides increased, high density lipoprotein decreased
Common (☐ 1/100, < 1/10)	Blood cholesterol increased, blood glucose increased, haematuria, proteinuria
Very Rare (☐ 1/10 000)	Blood creatine phosphokinase increased

The incidence of the adverse events was calculated from pooled clinical trial data involving 824 patients and from post-marketing data.

4.9 Overdose

Isotretinoin is a derivative of vitamin A. Although the acute toxicity of isotretinoin is low, signs of hypervitaminosis A could appear in cases of accidental overdose. Manifestations of acute vitamin A toxicity include severe headache, nausea or vomiting, drowsiness, irritability and pruritus. Signs and symptoms of accidental or deliberate overdosage with isotretinoin would probably be similar. These symptoms would be expected to be reversible and to subside without the need for treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Retinoid for treatment of acne.

ATC code: D10B A01

Mechanism of action

Isotretinoin is a stereoisomer of all-trans retinoic acid (tretinoin). The exact mechanism of action of isotretinoin has not yet been elucidated in detail, but it has been established that the improvement observed in the clinical picture of severe acne is associated with suppression of sebaceous gland activity and a histologically demonstrated reduction in the size of the sebaceous glands. Furthermore, a dermal anti-inflammatory effect of isotretinoin has been established.

Efficacy

Hypercornification of the epithelial lining of the pilosebaceous unit leads to shedding of corneocytes into the duct and blockage by keratin and excess sebum. This is followed by formation of a comedone and, eventually, inflammatory lesions. Isotretinoin inhibits proliferation of sebocytes and appears to act in acne by re-setting the orderly program of differentiation. Sebum is a major substrate for the growth of Propionibacterium acnes so that reduced sebum production inhibits bacterial colonisation of the duct.

5.2 Pharmacokinetic properties

Absorption

The absorption of isotretinoin from the gastro-intestinal tract is variable and dose-linear over the therapeutic range. The absolute bioavailability of isotretinoin has not been determined, since the compound is not available as an intravenous preparation for human use, but extrapolation from dog studies would suggest a fairly low and variable systemic bioavailability. When isotretinoin is taken with food, the bioavailability is doubled relative to fasting conditions.

Distribution

Isotretinoin is extensively bound to plasma proteins, mainly albumin (99.9 %). The volume of distribution of isotretinoin in man has not been determined since isotretinoin is not available as an intravenous preparation for human use. In humans little information is available on the distribution of isotretinoin into tissue. Concentrations of isotretinoin in the epidermis are only half of those in serum. Plasma concentrations of isotretinoin are about 1.7 times those of whole blood due to poor penetration of isotretinoin into red blood cells.

Metabolism

After oral administration of isotretinoin, three major metabolites have been identified in plasma: 4-oxo-isotretinoin, tretinoin, (all-trans retinoic acid), and 4-oxo-tretinoin. These metabolites have shown biological activity in several in vitro tests. 4-oxo-isotretinoin has been shown in a clinical study to be a significant contributor to the activity of isotretinoin (reduction in sebum excretion rate despite no effect on plasma levels of isotretinoin and tretinoin). Other minor metabolites includes glucuronide conjugates. The major metabolite is 4-oxo-isotretinoin with plasma concentrations at steady state, that are 2.5 times higher than those of the parent compound.

Isotretinoin and tretinoin (all-trans retinoic acid) are reversibly metabolised (interconverted), and the metabolism of tretinoin is therefore linked with that of isotretinoin. It has been estimated that 20-30 % of an isotretinoin dose is metabolised by isomerisation.

Enterohepatic circulation may play a significant role in the pharmacokinetics of isotretinoin in man. In vitro metabolism studies have demonstrated that several CYP enzymes are involved in the metabolism of isotretinoin to 4-oxo-isotretinoin and tretinoin. No single isoform appears to have a predominant role. Isotretinoin and its metabolites do not significantly affect CYP activity.

Elimination

After oral administration of radiolabelled isotretinoin approximately equal fractions of the dose were recovered in urine and faeces. Following oral administration of isotretinoin, the terminal elimination half-life of unchanged drug in patients with acne has a mean value of 19 hours. The terminal elimination half-life of 4-oxo-isotretinoin is longer, with a mean value of 29 hours.

Isotretinoin is a physiological retinoid and endogenous retinoid concentrations are reached within approximately two weeks following the end of isotretinoin therapy.

Pharmacokinetics in special populations

Since isotretinoin is contraindicated in patients with hepatic impairment, limited information on the kinetics of isotretinoin is available in this patient population. Renal failure does not significantly reduce the plasma clearance of isotretinoin or 4-oxo-isotretinoin.

5.3 Preclinical safety data

Acute toxicity

The acute oral toxicity of isotretinoin was determined in various animal species. LD50 is approximately 2000 mg/kg in rabbits, approximately 3000 mg/kg in mice, and over 4000 mg/kg in rats.

Chronic toxicity

A long-term study in rats over 2 years (isotretinoin dosage 2, 8 and 32 mg/kg/d) produced evidence of partial hair loss and elevated plasma triglycerides in the higher dose groups. The side effect spectrum of isotretinoin in the rodent thus closely resembles that of vitamin A, but does not include the massive tissue and organ calcifications observed with vitamin A in the rat. The liver cell changes observed with vitamin A did not occur with isotretinoin.

All observed side effects of hypervitaminosis A syndrome were spontaneously reversible after withdrawal of isotretinoin. Even experimental animals in a poor general state had largely recovered within 1–2 weeks.

Teratogenicity

Like other vitamin A derivatives, isotretinoin has been shown in animal experiments to be teratogenic and embryotoxic.

Due to the teratogenic potential of isotretinoin there are therapeutic consequences for the administration to women of a childbearing age (see section 4.3, section 4.4, and section 4.6).

Fertility

Isotretinoin, in therapeutic dosages, does not affect the number, motility and morphology of sperm and does not jeopardise the formation and development of the embryo on the part of the men taking isotretinoin.

Mutagenicity

Isotretinoin has not been shown to be mutagenic in *in vitro* or *in vivo* animal

tests.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule filling:

Beeswax, yellow;

Soya-bean oil, refined;

Soya-bean oil, hydrogenated;

Soya-bean oil, partially hydrogenated.

Capsule shell:

Gelatin;

Glycerol;

Karion 83 containing sorbitol, mannitol, hydrogenated hydrolysed starch;

Titanium dioxide E171;

Canthaxanthin pigment E161, containing gelatin, arachis oil (peanut oil), canthaxanthin, ascorbyl palmitate, α-tocopherol and silica.

Printing ink:

Shellac, refined;

Black iron oxide E172;

Titanium dioxide E171 (5 mg capsule only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Aluminium-aluminium blisters:

Do not store above 30 °C.

Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container

Aluminium-aluminium blister packs containing 30 capsules

6.6 Special precautions for disposal and other handling

Return any unused Roaccutane capsules to the Pharmacist

7. MARKETING AUTHORISATION HOLDER

Roche Products Limited

6 Falcon Way

Shire Park

Welwyn Garden City

AL7 1TW

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 00031/0158

PL 00031/0160

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

June 1983/July1997/December 2004

10. DATE OF REVISION OF THE TEXT

October 2006

LEGAL STATUS

POM

SUPPORTING INFORMATION

Patient Information Leaflet:
Roaccutane

Alternative format PIL:
Roaccutane (new window)

APPENDIX B

Roche Products Limited

Hexagon Place
6 Falcon Way
Shire Park
Welwyn Garden City
Hertfordshire
AL7 1TW

Telephone:	**+44 (0)1707 366 000**
Facsimile:	**+44 (0)1707 338 297**
WWW:	**http://www.rocheuk.com/**
Medical Information direct line:	**+44 (0)800 032 7298**
Customer Care direct line:	**+44 (0)800 731 5711**
Medical Information e-mail:	**roche@professionalinformation.co.uk**
Medical Information facsimile:	**+44 (0)1748 828801**

Document last updated on the *e*MC: **Wed 12 September 2007**

Neotigason 10mg & 25mg capsules

Table of Contents

1. NAME OF THE MEDICINAL PRODUCT
2. QUALITATIVE AND QUANTITATIVE COMPOSITION
3. PHARMACEUTICAL FORM
4. CLINICAL PARTICULARS
4.1 Therapeutic indications
4.2 Posology and method of administration
4.3 Contraindications
4.4 Special warnings and precautions for use
4.5 Interaction with other medicinal products and other forms of interaction
4.6 Pregnancy and lactation
4.7 Effects on ability to drive and use machines
4.8 Undesirable effects
4.9 Overdose
5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
5.2 Pharmacokinetic properties
5.3 Preclinical safety data
6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
6.2 Incompatibilities
6.3 Shelf life
6.4 Special precautions for storage
6.5 Nature and contents of container
6.6 Special precautions for disposal and other handling
7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Neotigason 10mg capsules

Neotigason 25mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsules with brown cap and white body with ROCHE printed in black on both cap and body, containing 10mg acitretin.

Capsules with brown cap and yellow body with ROCHE printed in black on both cap and body, containing 25mg acitretin.

Excipients include glucose (see section *4.3 Contraindications*).

For a full list of excipients, see section *6.1*.

3. PHARMACEUTICAL FORM

Capsules for oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe extensive psoriasis which is resistant to other forms of therapy.

Palmo-plantar pustular psoriasis.

Severe congenital ichthyosis.

Severe Darier's disease (keratosis follicularis).

4.2 Posology and method of administration

It is recommended that Neotigason be given only by, or under supervision of, a dermatological specialist.

Neotigason capsules are for oral administration.

The capsules should be taken once daily with meals or with milk.

There is a wide variation in the absorption and rate of metabolism of Neotigason. This necessitates individual adjustment of dosage. For this reason the following dosage recommendations can serve only as a guide.

Adults

Initial daily dose should be 25mg or 30mg for 2 to 4 weeks. After this initial treatment period the involved areas of the skin should show a marked response and/or side-effects should be apparent. Following assessment of the initial treatment period, titration of the dose upwards or downwards may be necessary to achieve the desired therapeutic response with the minimum of side-effects. In general, a daily dosage of 25 - 50mg taken for a further 6 to 8 weeks achieves optimal therapeutic results. However, it may be necessary in some cases to increase the dose up to a maximum of 75mg/day.

In patients with Darier's disease a starting dose of 10mg may be appropriate. The dose should be increased cautiously as isomorphic reactions may occur.

Therapy can be discontinued in patients with psoriasis whose lesions have improved sufficiently. Relapses should be treated as described above.

Patients with severe congenital ichthyosis and severe Darier's disease may require therapy beyond 3 months. The lowest effective dosage, not exceeding 50mg/day, should be given.

Continuous use beyond 6 months is contra-indicated as only limited clinical data are available on patients treated beyond this length of time.

Elderly

Dosage recommendations are the same as for other adults.

Children

In view of possible severe side-effects associated with long-term treatment, Neotigason is contra-indicated in children unless, in the opinion of the physician, the benefits significantly outweigh the risks.

The dosage should be established according to bodyweight. The daily dosage is about 0.5mg/kg. Higher doses (up to 1mg/kg daily) may be necessary in some cases for limited periods, but only up to a maximum of 35mg/day. The maintenance dose should be kept as low as possible in view of possible long-term side-effects.

Combination therapy

Other dermatological therapy, particularly with keratolytics, should normally be stopped before administration of Neotigason. However, the use of topical corticosteroids or bland emollient ointment may be continued if indicated.

When Neotigason is used in combination with other types of therapy, it may be possible, depending on the individual patient's response, to reduce the dosage of

Neotigason.

4.3 Contraindications

Neotigason is highly teratogenic. Its use is contra-indicated in pregnant women and women who might become pregnant during or within 2 years of the cessation of treatment (see section *4.4 Special warnings and special precautions for use*).

The use of Neotigason is contra-indicated in women who are breast feeding.

Neotigason is contra-indicated in patients with hepatic or renal impairment and in patients with chronic abnormally elevated blood lipid values.

Rare cases of benign intracranial hypertension have been reported after Neotigason and after tetracyclines. Supplementary treatment with antibiotics such as tetracyclines is therefore contra-indicated.

An increased risk of hepatitis has been reported following the concomitant use of methotrexate and etretinate. Consequently, the concomitant use of methotrexate and Neotigason should be avoided.

Concomitant administration of Neotigason with other retinoids or preparations containing high doses of Vitamin A, (i.e. more than the recommended dietary allowance of 4,000 - 5,000 i.u. per day) is contra-indicated due to the risk of hypervitaminosis A.

Neotigason is contra-indicated in cases of hypersensitivity to the preparation (acitretin or excipients) or to other retinoids.

Owing to the presence of glucose, patients with rare glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

Neotigason should only be prescribed by physicians who are experienced in the use of systemic retinoids and understand the risk of teratogenicity associated with acitretin therapy.

Neotigason is highly teratogenic. The risk of giving birth to a deformed child is exceptionally high if Neotigason is taken before or during pregnancy, no matter for how long or at what dosage. Foetal exposure to Neotigason always involves a risk of congenital malformation.

Neotigason is contra-indicated in women of childbearing potential unless the following criteria are met:

1. Pregnancy has been excluded before instituting therapy with Neotigason (negative pregnancy test within 2 weeks prior to therapy). Whenever practicable a monthly repetition of the pregnancy test is recommended during therapy.

2. She starts Neotigason therapy only on the second or third day of the next menstrual cycle.

3. Having excluded pregnancy, any woman of childbearing potential who is receiving Neotigason must practice effective contraception for at least one month before treatment, during the treatment period and for at least 2 years following its cessation.

Even female patients who normally do not practice contraception because of a history of infertility should be advised to do so, while taking Neotigason.

4. The same effective and uninterrupted contraceptive measures must also be taken every time therapy is repeated, however long the intervening period may have been, and must be continued for 2 years afterwards.

5. Any pregnancy occurring during treatment with Neotigason, or in the 2 years following its cessation, carries a high risk of severe foetal malformation. Therefore, before instituting Neotigason the treating physician must explain clearly and in detail what precautions must be taken. This should include the risks involved and the possible consequences of pregnancy occurring during Neotigason treatment or in the 2 years following its cessation.

6. She is reliable and capable of understanding the risk and complying with effective contraception, and confirms that she has understood the warnings.

In view of the importance of the above precautions, Neotigason Patient Information Leaflets are available to doctors and it is strongly recommended that these be given to all patients.

If oral contraception is chosen as the most appropriate contraceptive method for women undergoing retinoid treatment, then a combined oestrogen-progestogen formulation is recommended.

Patients should not donate blood either during or for at least one year following discontinuation of therapy with Neotigason. Theoretically there would be a small risk to a woman in the first trimester of pregnancy who received blood donated by a patient on Neotigason therapy.

Acitretin has been shown to affect diaphyseal and spongy bone adversely in animals at high doses in excess of those recommended for use in man. Since skeletal hyperostosis and extraosseous calcification have been reported following long-term treatment with etretinate in man, this effect should be expected with acitretin therapy.

Since there have been occasional reports of bone changes in children, including premature epiphyseal closure, skeletal hyperostosis and extraosseous calcification after long-term treatment with etretinate, these effects may be expected with acitretin. Neotigason therapy in children is not, therefore, recommended. If, in exceptional circumstances, such therapy is undertaken the child should be carefully monitored for any abnormalities of musculo-skeletal development.

In adults receiving long□term treatment with Neotigason, appropriate examinations should be periodically performed in view of possible ossification abnormalities (see section *4.8 Undesirable effects*). Any patients complaining of atypical musculo-skeletal symptoms on treatment with Neotigason should be promptly and fully investigated to exclude possible acitretin-induced bone changes. If clinically significant bone or joint changes are found, Neotigason therapy should be discontinued.

The effects of UV light are enhanced by retinoid therapy, therefore patients should avoid excessive exposure to sunlight and the unsupervised use of sun lamps.

Hepatic function should be checked before starting treatment with Neotigason, every 1 - 2 weeks for the first 2 months after commencement and then every 3 months during treatment. If abnormal results are obtained, weekly checks should be instituted. If hepatic function fails to return to normal or deteriorates further, Neotigason must be withdrawn. In such cases it is advisable to continue monitoring hepatic function for at least 3 months.

Serum cholesterol and serum triglycerides (fasting values) must be monitored, especially in high□risk patients (disturbances of lipid metabolism, diabetes mellitus, obesity, alcoholism) and during long□term treatment.

In diabetic patients, retinoids can alter glucose tolerance. Blood sugar levels should therefore be checked more frequently than usual at the beginning of the treatment period.

Patients should be warned of the possibility of alopecia occurring (see section *4.8 Undesirable effects*).

4.5 Interaction with other medicinal products and other forms of interaction

Existing data suggests that concurrent intake of acitretin with ethanol led to the formation of etretinate. However, etretinate formation without concurrent alcohol intake cannot be excluded. Therefore, since the elimination half-life of etretinate is 120 days the post-therapy contraception period in women of childbearing potential must be 2 years (see section *4.4 Special warnings and precautions for use).*

An increased risk of hepatitis has been reported following the concomitant use of methotrexate and etretinate. Consequently, the concomitant use of methotrexate and Neotigason should be avoided (see section *4.3 Contra-indications).*

In concurrent treatment with phenytoin, it must be remembered that Neotigason partially reduces the protein binding of phenytoin. The clinical significance of this is as yet unknown.

Interaction studies show acitretin does not interfere with the anti-ovulatory action of the combined oral contraceptives.

Interactions between Neotigason and other substances (e.g. digoxin, cimetidine)

have not been observed to date.

4.6 Pregnancy and lactation

Neotigason is contra-indicated during pregnancy as it is a known human teratogen.

The use of Neotigason is contra-indicated in women who are breast feeding. It is also contra-indicated in women of childbearing potential unless specific criteria are met, (see section *4.4 Special warnings and special precautions for use*).

4.7 Effects on ability to drive and use machines

Decreased night vision has been reported with Neotigason therapy. Patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night. Visual problems should be carefully monitored (see section *4.8 Undesirable effects*).

4.8 Undesirable effects

Most of the clinical side-effects of Neotigason are dose-related and are usually well-tolerated at the recommended dosages. However, the toxic dose of Neotigason is close to the therapeutic dose and most patients experience some side-effects during the initial period whilst dosage is being adjusted. They are usually reversible with reduction of dosage or discontinuation of therapy.

The skin and mucous membranes are most commonly affected, and it is recommended that patients should be so advised before treatment is commenced.

*Skin:*Dryness of the skin may be associated with scaling, thinning, erythema (especially of the face) and pruritus. Palmar and plantar exfoliation may occur. Sticky skin and dermatitis occur frequently. Epidermal fragility, nail fragility and paronychia have been observed.

Occasionally bullous eruptions and abnormal hair texture have been reported. Hair thinning and frank alopecia may occur, usually noted 4 to 8 weeks after starting therapy, and are reversible following discontinuation of Neotigason. Full recovery usually occurs within 6 months of stopping treatment in the majority of patients.

Granulomatous lesions have occasionally been observed.

Sweating has been reported infrequently.

Rarely, patients may experience photosensitivity reactions.

Mucous membranes: Dryness of mucous membranes, sometimes with erosion, involving the lips, mouth, conjunctivae and nasal mucosa have been reported. Corneal ulcerations have been observed rarely.

Dryness of the conjunctivae may lead to mild-to-moderate conjunctivitis or xerophthalmia and result in intolerance of contact lenses; it may be alleviated by lubrication with artificial tears or topical antibiotics.

Cheilitis, rhagades of the corner of the mouth, dry mouth and thirst have occurred. Occasionally stomatitis, gingivitis and taste disturbance have been reported.

Rhinitis and epistaxis have been observed.

*Central nervous system:*Headache has occurred infrequently. Benign intracranial hypertension has been reported. Patients with severe headache, nausea, vomiting and visual disturbance should discontinue Neotigason immediately and be referred for neurological evaluation and care.

Neuro-sensory system: Blurred or decreased night vision has been reported occasionally.

Musculo-skeletal system: Myalgia and arthralgia may occur and be associated with reduced tolerance to exercise. Bone pain has also been reported.

Maintenance treatment may result in hyperostosis and extraskeletal calcification, as observed in long-term systemic treatment with other retinoids.

Gastrointestinal tract: Nausea has been reported infrequently. Vomiting, diarrhoea and abdominal pain have been observed rarely.

*Liver and biliary system disorders:*Transient, usually reversible elevation of serum levels of liver enzymes may occur. When significant, dosage reduction or discontinuation of therapy may be necessary. Jaundice and hepatitis have occurred rarely.

Metabolic: Elevation of serum triglycerides above the normal range has been observed, especially where predisposing factors such as a family history of lipid disorders, obesity, alcohol abuse, diabetes mellitus or smoking are present. The changes are dose-related and may be controlled by dietary means (including restriction of alcohol intake) and/or by reduction of dosage of Neotigason. Increases in serum cholesterol have occurred.

Cardiovascular system: Occasionally peripheral oedema and flushing have been reported.

*Miscellaneous reactions:*Increased incidence of vulvo-vaginitis due to Candida albicans has been noted during treatment with acitretin. Malaise and drowsiness have been infrequently reported.

4.9 Overdose

Manifestations of acute Vitamin A toxicity include severe headache, nausea or vomiting, drowsiness, irritability and pruritus. Signs and symptoms of accidental or deliberate overdosage with Neotigason would probably be similar. They would be expected to subside without need for treatment.

Because of the variable absorption of the drug, gastric lavage may be worthwhile within the first few hours after ingestion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Retinol (Vitamin A) is known to be essential for normal epithelial growth and differentiation, though the mode of this effect is not yet established. Both retinol and retinoic acid are capable of reversing hyperkeratotic and metaplastic skin changes. However, these effects are generally only obtained at dosages associated with considerable local or systemic toxicity. Acitretin, a synthetic aromatic derivative of retinoic acid, has a favourable therapeutic ratio, with a greater and more specific inhibitory effect on psoriasis and disorders of epithelial keratinisation. The usual therapeutic response to acitretin consists of desquamation (with or without erythema) followed by more normal re-epithelialisation.

Acitretin is the main active metabolite of etretinate.

5.2 Pharmacokinetic properties

Absorption

Acitretin reaches peak plasma concentration 1 - 4 hours after ingestion of the drug. Bioavailability of orally administered acitretin is enhanced by food. Bioavailability of a single dose is approximately 60%, but inter-patient variability is considerable (36 □ 95%).

Distribution

Acitretin is highly lipophilic and penetrates readily into body tissues. Protein binding of acitretin exceeds 99%. In animal studies, acitretin passed the placental barrier in quantities sufficient to produce foetal malformations. Due to its lipophilic nature, it can be assumed that acitretin passes into breast milk in considerable quantities.

Metabolism

Acitretin is metabolised by isomerisation into its 13□cis isomer (*cis* acitretin), by glucuronidation and cleavage of the side chain.

Elimination

Multiple-dose studies in patients aged 21 □ 70 years showed an elimination half□life of approximately 50 hours for acitretin and 60 hours for its main metabolite in plasma, *cis* acitretin, which is also a teratogen. From the longest elimination half□life observed in these patients for acitretin (96 hours) and *cis* acitretin (123 hours), and assuming linear kinetics, it can be predicted that more than 99% of the drug is eliminated within 36 days after cessation of long□term

therapy. Furthermore, plasma concentrations of acitretin and *cis* acitretin dropped below the sensitivity limit of the assay (< 6ng/ml) within 36 days following cessation of treatment. Acitretin is excreted entirely in the form of its metabolites, in approximately equal parts via the kidneys and the bile.

5.3 Preclinical safety data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Glucose, liquid, spray-dried

Sodium ascorbate

Gelatin

Purified water

Microcrystalline cellulose

Capsule shell:

Gelatin

Iron oxide black (E172)

Iron oxide yellow (E172)

Iron oxide red (E172)

Titanium dioxide (E171)

Printing ink:

Shellac

N-Butyl alcohol

Isopropyl alcohol

Propylene glycol

Ammonium hydroxide

Iron oxide black (E172)

6.2 Incompatibilities

None.

6.3 Shelf life

Neotigason capsules have a shelf-life of 3 years.

6.4 Special precautions for storage

Store in the original package. Do not store above 25°C.

6.5 Nature and contents of container

All aluminium blisters containing 56 capsules.

PVC/PVDC (Duplex) or PVC/PE/PVDC (Triplex) blisters with aluminium cover foil containing 56 or 60 capsules.

Amber glass bottles with metal screw caps containing 30 or 100 capsules.

6.6 Special precautions for disposal and other handling

None.

7. MARKETING AUTHORISATION HOLDER

Roche Products Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, United Kingdom.

8. MARKETING AUTHORISATION NUMBER(S)

PL 0031/0262

PL 0031/0263

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8 June 1992

10. DATE OF REVISION OF THE TEXT

August 2007

Neotigason is a registered trade mark

Files/OLK98/Neotigason 10mg 25mg capsules SPC from the eMC.htm

SUPPORTING INFORMATION

Patient Information Leaflet:
Neotigason 10mg & 25mg Capsules

Alternative format PIL:
Neotigason 10mg & 25mg Capsules (new window)

Medicine Guide:
Neotigason (new window)